# THE LURE OF MEDICAL HISTORY†

## PURKINJE'S PIONEER SELF-EXPERIMENTS IN PSYCHOPHARMACOLOGY*

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PART II**

THUS Purkinje's unusually clear description and correct interpretation of these interesting side actions of digitalis, over a century ago, are strictly in accordance with those of the present day and will probably hold for all time. Today records of these side actions on vision in the clinical use of digitalis are a commonplace, but their relationship to the drug's actions was not suspected or recognized until 1925, when they were rediscovered and brought to the attention of the medical profession. While these side actions are important clinically as a warning of beginning toxicity from digitalis, the so-called "minor toxicity symptoms," for Purkinje they were essentially manifestations of a disturbed physiology. He proved by his experiments that digitalis did not create directly those flickerings in the eye, but rather indirectly by mediation through some other physiological function; in this case nausea and emesis. For drugs do not create new physiological functions; they only affect those existing. Thus, Purkinje was always intrigued by other means or possibilities of probing deeper into an understanding of physiological function. He was probably well aware that he was laying down at the same time a more secure foundation for pharmacology. His drug experiments were not mere by-products of physiology. This seems to be indicated in his most interesting paper entitled, "Einige Beiträge zur physiologischen Pharmacologie," published in 1829.[7] It deals with interesting effects from drug combinations, which I may discuss next.

### SELF-EXPERIMENTS WITH DRUG COMBINATIONS

In his paper on physiological pharmacology, Purkinje has declared his preference for self-experiments in pharmacology. His object is to reveal all actions, especially the subjective, which cannot be tested on animals. First, he determined results with some individual drugs which entered into certain combinations.

*Camphor.*—After taking 6 grains (0.4 gram) of gum camphor by mouth, Purkinje experienced only an oppressive burning sensation in the stomach, but 12 grains (0.8 gram) caused him to remain in bed. About fifteen minutes after the initial gastric irritation, he felt a sensation of warmth of the entire skin, and nerve irritation was marked, especially in muscle and skin nerves, with prickling of skin. Sensitivity to external environment was decreased somewhat, with a sensation of hairiness. Respiration was unusually easy and free. His mental activity was increased considerably, so that thinking seemed to be clearer. A camphor euphoria was experienced, spiritual thoughts and consciousness being increased. The leading spiritual thought was that man in his being was a superman and his calling was the liberation of his brothers.

His whole life was laid before him without a relationship to his presence, which he believed completely overlooked. This state lasted one and one-half hours, and then was lost in ordinary thoughts and duties without the slightest feeling of anxiety. Afterward, his head was not the least affected, which, however, is the case after other kinds of euphoria or sprees. This experiment was not repeated, but he thought it would be interesting and important to know if a state of exalted feeling occurred in different individuals. Probably the exalted state would soon be lost. To him it seemed important that this experience was not unlike some forms of insanity. The action disappeared rapidly just like ether, nitrous oxid and other volatile agents. It was remarkable to him that no trace of action remained afterward. Excretion of camphor occurred in the lungs and sweat, and a trace in urine. The blood apparently took up the drug and brought it to the brain and nerves. He suggested that the external temperature may cause a significant difference in the action of camphor when the skin and pulmonary volatilization is retarded.

In a final experiment with camphor, Purkinje took at once two scruples (40 grains, or 2.6 grams) with the same subjective experiences. There was also increased muscular activity, movements being easily executed, but the muscle power was unchanged. He was unable to concentrate while writing. No religious exaltation was felt as in the first experiment. He lost consciousness of his personality, felt exhausted, and required orientation with surroundings, but all this was lost in a stream of peculiar thoughts. The sensations were like those of a drunkard who calls himself names, mutters, and has moments of normal behavior. He states that he expectorated camphor in saliva and sputum. The subjective sensations increased to the point of emesis which, however, did not materialize. An hour appeared an inordinately long time, as in a dream. A similar experience was observed by Kant in his ripe old age, when an hour's walk seemed to be a long journey.

*Opium Nostras.*—Purkinje tested this opium because it was reported to be one-fifth as strong as the oriental variety. In a small quantity it acted to prevent the stupor of wine. He suggested that perhaps this action explained its effectiveness in delirium tremens.

*Belladonna.*—Half an hour after Purkinje took twenty drops of an extract of belladonna on sugar, there was dryness of the nose and mouth. There was a feeling of anxiety in the precordial region and sometimes the pulse was full. Contractions were felt in the urinary passages, and urine was scanty. Beef soup tasted sour, and afterward there

† A Twenty-Five Years Ago column, made up of excerpts from the official journal of the California Medical Association of twenty-five years ago, is printed in each issue of CALIFORNIA AND WESTERN MEDICINE. The column is one of the regular features of the Miscellany department, and its page number will be found on the front cover.

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** Part I of this paper was printed in CALIFORNIA AND WESTERN MEDICINE, July, 1938, on page 52.

was a peculiar taste of senega. This was not due to the food eaten, because other dietary articles gave the same sensations. Dry bread tasted peculiar when chewed. These peculiar oral sensations were due to absence of saliva and mucus, their presence contributing normal sensations. All actions of belladonna were due to the decreased secretions.

A hypochondriac individual, whom Purkinje knew for some time, experienced the same sensations as did Purkinje after the belladonna. So he tried treatment of this state with homeopathic doses of belladonna and thought he observed a beneficial action in a way which, however, could have an explanation in the variability of the disease.

*Stramonium.*—This drug gave similar effects to those of belladonna, with this difference, that an alcoholic extract of the seeds caused depression, that is, a narcotic action. This he had never observed with belladonna, but both drugs caused dilatation of the pupils. Today stramonium is used in excitatory states, like Parkinsonian disease and the like.

*Turpentine, With and Without Alcohol.*—First, Purkinje took one dram (60 minims, or 4 cubic centimeters) of turpentine on sugar every morning with unpleasant sensations in the alimentary tract, but he could sleep off the effects with one hour's sleep daily. He slept better both day and night, there being quieter and calmer sleep after turpentine. He thought it might be used as a hypnotic in certain cases.

He felt an unusual experience when he took a glass of wine with the turpentine, which was not felt after wine alone. An unusual euphoria occurred, due not to a specific action, *i. e.,* previous depression of the central nervous system by the turpentine, and the action lasted several days. With pure turpentine a dizziness occurred, but not after taking a mixture of alcohol and ten drops of turpentine. He thought this mixture might be suited to some individuals under treatment (alcoholic intoxication?).

*Narcotic Action of Oil of Nutmeg.*—Purkinje's results with turpentine suggested trials with this volatile oil. One morning he ate a nutmeg with sugar, which was not unpleasant; yet he felt a weariness and a sense of depression which lasted a whole day, though not disturbing mentally. But he noticed, after taking a small glass of table wine, that the nutmeg affected him very much.

One afternoon, after dinner, Purkinje ate three nutmegs. The action came on rapidly. There was marked sleepiness with pleasant dreams, which were disturbed occasionally by some restlessness. Finally, he laid down on a sofa to sleep. He states: "At half-past six (in October), when it was almost dark, I woke up in order to go to the Royal Theater in Brüder Street (Berlin) where I lived. The distance was long, but this time I thought it had *no end.* My movements appeared entirely adequate, but were lost momentarily in dream pictures, from which I had to extricate myself with considerable force in order to keep on walking. My feet did their duty, and, since I had to stick to a straight road, there was no danger of going astray. I went forward in this dream, for, if I attempted to orient myself, I could not even recognize the cross streets. Time seemed long. I got to the opposite side of the place where I was going. During this time dreams and physical activity battled one another. The return journey was good, and I slept well that night and next day." *But the wine acted on him more powerfully than usual for several days.*

In his next experiment, Purkinje rubbed up two drams (120 grains, or 8 grams) of nutmegs with pure brandy and drank the extract; the action was different. Instead of a quiet narcosis, there was muscular restlessness and dizziness. This was due to an internal action of the nutmeg in this combined form. This oil, turpentine, and all volatile oils act on the cerebrum and cerebellum. Combined with alcohol they affect the motor functions more, so that the actions of aqueous and alcoholic mixtures should be different. Pharmacodynamically, the action is less chemical than on the organism, *where an agent increases the disposition to the action of another drug.* He regretted that he could not investigate the effects of coffee or tea on different drugs, because his scientific interests became diverted. But Purkinje had no doubt that observations in this field would throw light on many problems. Equally important was a cautious attitude which he expressed. He said that the few experiments he could make should be repeated on a large number of individuals so as to give a correct general result; this, in order to establish subjective results as soundly as the objective, and not leave them merely empirical.

As regards Purkinje's self-experiments with nutmeg, essentially the same symptoms in the early stages of nutmeg poisoning were described seventy-eight years later by the late Professor Cushny,[8] who was apparently unaware of Purkinje's description. Two years after Cushny's report, Dale,[9] who reviewed reports of clinical actions and poisoning from oil of nutmeg, and undertook experiments with the oil on cats without success, also did not refer to Purkinje's self-experiments. In his Alpha Omega Alpha Lecture on Leeuwenhoek in 1933, before the California-Stanford chapters, Professor A. W. Meyer, professor of anatomy at Stanford, discussed certain pharmacological experiments with nutmeg on mites by this microscopist; he also referred to them in a recent article.[14] Mites were exposed to pieces of nutmeg in a glass tube; these would approach the nutmeg and then rebound as they came closer. If they remained very close, they died (narcosis and paralysis?). This was about 1676, so that Leeuwenhoek preceded by something like 153 years Purkinje's self-experiments with nutmeg.

## COMMENT

To return to Purkinje's results with drug combinations, he seems to have been the first one to recognize that drugs can affect each other's actions. In other words, Purkinje discovered the allergic state. More than that, he demonstrated it on himself. He actually showed a sensitization on himself to two drugs as the result of taking another drug. That is, an habitual glass of wine (weak

alcoholic beverage), without action itself, increased his reactions to turpentine and to nutmeg. This can be regarded as a case of potentiation of action on drugs by another drug. Besides making a clear demonstration of allergy, Purkinje also suggested the correct explanation of the phenomenon. He concluded that these drugs did not react with each other directly, and thus did not alter their actions in a chemical sense, but that the changes were produced by some effects on physiological functions. What apparently puzzled him was that a drug whose action was no longer expressed could still influence the actions of other drugs so markedly. However, this puzzle is still unsolved today. Nevertheless, it must be granted that Purkinje demonstrated long ago that conditions influence the actions of drugs, something now universally recognized, but he is never credited with this discovery.

### EXPERIMENTS ON CILIA

Before closing, I cannot forego the mention of Purkinje's original pharmacological experiments on cilia in 1835.[10] These were done with his favorite pupil, Valentin. In this work there are presented a table and discussion of results with fifty-five chemical agents and drugs which acted on ciliary motion. Among other phenomena, Purkinje and Valentin recognized that organic acids (acetic and others) affected cilia more quickly and readily than inorganic acids (HCl and others). Eighty years later Olmsted and MacArthur[11] described exactly the same differences; in fact, used the same acids on frog cilia without apparently being aware of Purkinje's and Valentin's experiments. The only difference was in the method of expressing the strength of the acids, *i. e.,* use of $p_H$ by Olmsted and MacArthur. Purkinje made this clever deduction: Since hydrocyanic acid and strychnin do not poison cilia, these structures do not belong to the central nervous system. Another deduction in a similar vein, but having nothing to do with cilia, was as follows: Frogs killed with narcotics are not entirely dead, since the muscles and nerves of their bodies respond to direct stimuli. This was really clever for those exclusively anatomical days. As a result, Purkinje was called a "physiological anatomist."

### IN CONCLUSION

It can be said of Purkinje what has been said before by others—the genius of the great master, Purkinje, has remained undeservedly obscure. And what do you suppose this self-effacing supermaster of physiology is reported to have said on New Year's Day, 1869, the year of his death (age, eighty-two years)?

"I have indeed discovered various things, but, as for immortality of my name, this should not be taken literally. A hundred years hence perhaps only a few will know who Purkinje was. But that makes no difference. For indeed we do not know who discovered the plow, and yet it serves all humanity. The cause remains the same, but not the name—and that is the important thing" (Hykes[12]).

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## CLINICAL NOTES AND CASE REPORTS

### PSEUDO-PROPTOSIS FROM SUBCONJUNCTIVAL TUMORS

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MUCH has been written about false exophthalmos due to orbital tumors and its diagnostic complications. Here is a case of subconjunctival lipomas with a desiccating keratitis.

### REPORT OF CASE

Mr. Ira B., colored, age fifty-one, was referred to the Monterey County Hospital on November 1, 1937, with a diagnosis of bilateral tumors of the lachrymal glands. He complained of failing vision in the right eye, with excessive weeping of several weeks' duration. The patient stated that the eyes had always been prominent, but that the swellings on the upper and outer portions of the eyeballs had been noticeable since 1918.

There had been no symptoms referable to the eyes until the present complaint. No severe illnesses or childhood diseases were remembered. Vision had always been good and the eyes had never been examined. Venereal infection was denied.

*Examination:*

Vision: Right, 20/65. Jaeger iii at 15 inches. Left, 20/20. Jaeger ii at 15 inches.

There was a marked proptosis in both eyes, slightly more on the right. The lids were very loosely applied to the globes. Lachrymal glands were easily seen projecting slightly below the orbital rim. Both eyes showed a yellow-